IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: M. Moezie **Art Unit: 1617**

In RE:	**Application of Michael DITTGEN, et al**
Ser.No.:	**08/738,314** (parent)
Filed:	**October 25, 1996**

DECLARATION FILED TO HELP OVERCOME REJECTION UNDER 35 U.S.C. 103

Hon. Commissioner of Patents and Trademarks,
Washington, D. C. 20231

Sir:

In response to the Office Action dated July 21, 1999, please consider the following comparative evidence of unexpectedly better performance:

WHEREAS, WE, Michael DITTGEN, Sabine FRICKE, Herbert HOFFMANN, Claudia MOORE, Michael OETTEL and Monika OSTERTAG, citizens of Germany, whose post office addresses and residencies are, respectively, Heidenberg 35/37, Apolda, Germany 99510; An der Riese 16, Jena, Germany 07749; Treunertstrasse 12, Jena, Germany 07749; Zur Lämmerlaide 15, Jena, Germany 07751; Beethovenstrassé 30, 07743 Jena, Germany; and Haussenstrasse 14, Göttingen, Germany 37073; have made application for Letters Patent for an improved, new and useful

COMBINATION PREPARATION FOR CONTRACEPTION BASED ON NATURAL ESTROGENS

in a U.S.Patent Application, as identified hereinabove, of which claims 8, 10, 11, 12 and 14 were rejected as obvious under 35 U.S.C. 103 over the Embase abstract 272 (Darney) in view of the WPIDS abstract -924 (DE 4104285), DE 4224534, WPIDS abstract -225 (WO 95/07081), Pasquale (AA), Guengerich (AT) and Zhu.

ONLY discussions to claims 1-7 are relevant

WHEREAS I, hereby affirm that the method of contraception claimed in amended claims 12 and 14 and new claim 16 (of the accompanying amendment filed on or about January 7, 2000) and the contraceptive preparation claimed in amended claims 8, 10 and new claim 15 (of the accompanying amendment filed on or about January 7, 2000) are unexpectedly and surprisingly better than the methods and preparations disclosed and suggested in DE 42 24 534 A1, published January 27, 1994, M. Ehrlich and H. Kuhl, inventors; and by DE 41 04 385 C1, published and granted August 13, 1992, M. Ehrlich and H. Kuhl, inventors.

WHEREAS I, hereby affirm that the method of contraception claimed in amended claims 12 and 14 and new claim 16 (of the accompanying amendment filed on or about January 7, 2000) and the contraceptive preparation claimed in amended claims 8, 10 and new claim 15 (of the accompanying amendment filed on or about January 7, 2000) is significantly more effective in preventing ovulation in all stages of treatment than the methods and preparations disclosed and suggested in DE 42 24 534 A1, published January 27, 1994, M. Ehrlich and H. Kuhl, inventors; and by DE 41 04 385 C1, published and granted August 13, 1992, M. Ehrlich and H. Kuhl, inventors.

WHEREAS I, hereby affirm that the method of contraception claimed in amended claims 12 and 14 and new claim 16 (of the accompanying amendment filed on or about January 7, 2000) and the contraceptive preparation claimed in amended claims 8, 10 and new claim 15 (of the accompanying amendment filed on or about January 7, 2000) unexpectedly and surprisingly produce significantly less intracyclic bleeding in fewer individuals than the methods and preparations disclosed and suggested in DE 42 24 534 A1 published January 27, 1994, M. Ehrlich and H. Kuhl, inventors; and by DE 41 04 385 C1, published and granted August 13, 1992, M. Ehrlich and H. Kuhl, inventors, while providing more effective cycle control.

I. Preparations Studied

1. Prior Art Method of Administration and Contraceptive Preparation

The prior art comparative preparation included a seven day first stage in which estrogen (equivalent to estradiol valerate, 2 mg) alone was administered and a subsequent 21 day second stage in which a combination of estrogen and progestin (equivalent to estradiol valerate 2 mg; + cyproterone acetate 2 mg) was administrated. The prior art preparations were based on DE 42 24 534 A1, published January 27, 1994, M. Ehrlich and H. Kuhl, inventors; and by DE 41 04 385 C1, published and granted August 13, 1992, M. Ehrlich and H. Kuhl, inventors. The contraceptive preparation of the prior art was administered to healthy
fertile women.

2. Method of Administration and Contraceptive Preparation according to The Invention as Claimed in Amended Claims 8, 10, 12 and 14 and New claims 15 and 16

The contraceptive preparation of the invention contains 3 days of estrogen (estradiol valerate, 3 mg) alone, 4 days of a combination of estrogen and progestin (estradiol valerate, 2 mg, + dienogest, 1 mg), 16 days of another combination of estrogen and progestin (estradiol valerate, 2 mg, + dienogest, 2 mg), 2 days of estrogen alone (1 mg estradiol valerate) and finally 3 days of a placebo. The contraceptive preparation of the invention was administered to healthy fertile women.

II. COMPARATIVE STUDY OF INTRACYCLIC BLEEDING

1. Methods

The main target variable was the amount of intracyclic bleeding which occurred during the 2nd and the 4th pill-taking cycles. Intracyclic bleeding was defined in the study protocols as bleeding of any intensity on days 4 to 21 during the estrogen/progestin combination stages. Exploratory analysis of bleeding pattern using the reference period recommended by the WHO was performed. The contraceptive preparation of the prior art was administered to 466 healthy fertile women, the preparation of the invention to 100 healthy fertile women.

2. Intracyclic Bleeding Results

The results of the analysis of the primary target variable are summarized in the following table 1.

Table 1: Results of Analysis of the Primary Target Variable Subjects with at least one Intracyclic Bleeding During the 2nd and 4th Cycles

Prior Art Preparation 1 (N=466)		Preparation 2 (invention) (N=100)	
Number Bleeding, n	%	Number Bleeding, n	%
350	75.11	47	47

N = total number of test subjects

There is a significant large difference in the percentage of subjects experiencing intracyclic bleeding during cycles 2 to 4 between the preparation of the invention and the closest prior art represented by DE 42 24 534 A1 and DE 41 04 385 C1.

Furthermore as seen from the results below preparation 2 of the invention has better cycle control with a lower number of subjects (almost half the number that suffer bleeding in the case of the prior art preparation) suffering from intracyclic bleeding events.

III. COMPARATIVE CONTRACEPTIVE EFFICIENCY STUDIES

1. Methods

The same preparations and methods were used as in the bleeding study except that the prior art preparation was administered to 21 test subjects (healthy fertile women) and the preparation of the invention was administered to 25 test subjects (healthy fertile women). The main target variable of this second comparative study was the ovulation inhibition assessed according to the "ovarian activity grading" method during every second day during one pre-cycle, 3 treatment cycles and one post-treatment cycle. The ovarian activity grading method is described in the following Table II.

Table II: Ovarian Activity Grading Method

			HORMONES	
GRADE	**meaning**	**FLS mm**	**Estradiol, nmol/l**	**Progesterone, nmol/l**
1	No activity	< 10		
2	Potential activity	> 10		
3	Non active FLS	> 13	≤ 0.1	
4	Active FLS	> 13	> 0.1	< 5
5	LUF	> 13, persisting	> 0.1	> 5
6	Ovulation	> 13, ruptured	> 0.1	> 5

The following describes the meaning and the definition of the abbreviations in Table II:

0.1 nmol/l = 30 pg/ml estradiol

5 nmol/l = 1.6 ng/ml progesterone

FLS= follicle like structure

LUF = lutainized unruptured follicle

The serum hormone levels were determined by radioimmunoassay and the follicular diameter was determined by vaginal ultrasound measurements every other day during a pre-cycle, three treatment cycles and a post-treatment cycle.

2. Results

The following table III summarizes the results of the comparative contraceptive efficiency study. The frequency of subjects in each graded category of ovarian activity was determined for each cycle. The following Table III shows the number of subjects, n, in each graded category in each cycle out of the total number of test subjects (N = 21 for the invention; N = 24 for the prior art) for that preparation that showed that activity.

Table III. The Results of the Analysis of the Primary Target Variable in the Comparative Contraceptive Efficiency Tests; Ovarian Activity Grade During Pre-treatment Cycle, Three Treatment Cycles and Post-treatment Cycle

Grading	Preparation I (Prior Art, N=25) Cycles					Preparation II (Invention, N=21) Cycles				
	pre	T1	T2	T3	post	pre	T1	T2	T3	post
cycle not assessable	1	0	1	3	3	0	0	0	0	0
1 =no activity	0	18	17	13	0	0	4	2	3	0
2=potential activity	0	2	3	4	0	0	8	10	9	0
3=nonactive FLS	0	0	2	1	0	0	0	0	0	0
4=active FLS	0	4	2	4	1	0	7	4	6	0
5=LUF	0	0	0	0	1	0	2	5	3	2
6=ovulation	24	1	0	0	20	21	0	0	0	19

FLS = follicle-like structure

LUF= lutainized unruptured follicle

T = Treatment cycle

Regarding ovulation inhibition as marker of the contraceptive efficacy there are significant differences between the preparations. Administration of preparation 1 (prior art) produces an ovulation during the 1st treatment cycle (T1), however preparation II (invention) effectively inhibits ovulation during all treatment cycles (T1,T2,T3). The distribution of the grading for the preparation II (invention) is comparable to usual oral contraceptives containing ethynyl etradiol in an amount of 20 or 30 µg and a progestin in a sufficient amount.

Preparation	Treatment Cycle	% patients with grading 4, 5
Ethynyl estradiol 20 µg + Gestodene 75 µg	1	20
	2	37
	3	40
Ethynyl estradiol 20 µg + Levonorgestrel 100 µg	1	8
	2	50
	3	37
Ethynyl estradiol 30 µg + Dienogest 2 mg	1	5
	2	40
	3	50
Preparation II (Invention)	1	33
	2	43
	3	43

Therefore it can be concluded that preparation II (invention) is a safe preparation which effectively inhibits ovulation.

IV. CONCLUSION

Administration of a contraceptive preparation according to amended claims 8, 10, 12 and 14 and new claims 15 and 16 that is even more effective in preventing ovulation than a corresponding prior art preparation according the cited DE references provides an unexpected and surprising reduction in the amount of intracyclic bleeding. This is in direct contradiction to the stated results in the DE references, which state that it is necessary to use the method and preparation of their invention to obtain a significant reduction in intracyclic bleeding.

I HEREBY DECLARE AND AFFIRM THAT ALL STATEMENTS made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the above-named application, any patent issuing thereon, or any patent to which this Declaration is directed.

DATE:

23.02.00 — Michael DITTGEN

21.02.00 — Sabine FRICKE

20/03/00 — Herbert HOFFMANN

21.02.00 — Claudia MOORE

21.02.00 — Michael OETTEL

25.03.2000 — Monika OSTERTAG